Correlations Between Creutzfeldt-Jakob Disease (CJD) and the Endocrine System

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Abstract

Creutzfeldt-Jakob disease (CJD) is a rare, degenerative brain disorder caused by abnormal proteins referred to as “prions" that accumulate in one’s brain. This life-threatening disease leads to individuals contracting symptoms such as memory loss, personality changes, and impaired judgment. As the disease progresses, the body starts experiencing blindness, weakness, and involuntary movements that typically lead to death within six to eight months. There are three primary divisions: Sporadic Creutzfeldt-Jakob disease (sCJD), Familial Creutzfeldt-Jakob disease (fCJD), and Acquired Creutzfeldt-Jakob disease (aCJD).

This is the first study to explore and recognize the correlation of CJD on the human body's endocrine system. By analyzing MRI scans and plotting data to create graphs, the research team has identified notable disruptions in the normal secretion of hormones from the hypothalamus and pituitary gland. This shows significant implications for the reproductive health, metabolic function, and overall endocrine balance of affected individuals. Specifically, the disease can result in delayed or altered puberty, infertility, and metabolic dysfunction.

Upon discovering this pattern, the study moved forward with a focus on what factors are contributing to the disruptions in hormone secretion. The research team then created a simulation using Python code to model trends associated with current CJD cases and predicted several variables in the succeeding years. They compared the trends that were modeled to the new trends associated with implementing our potential methods for mitigating CJD.

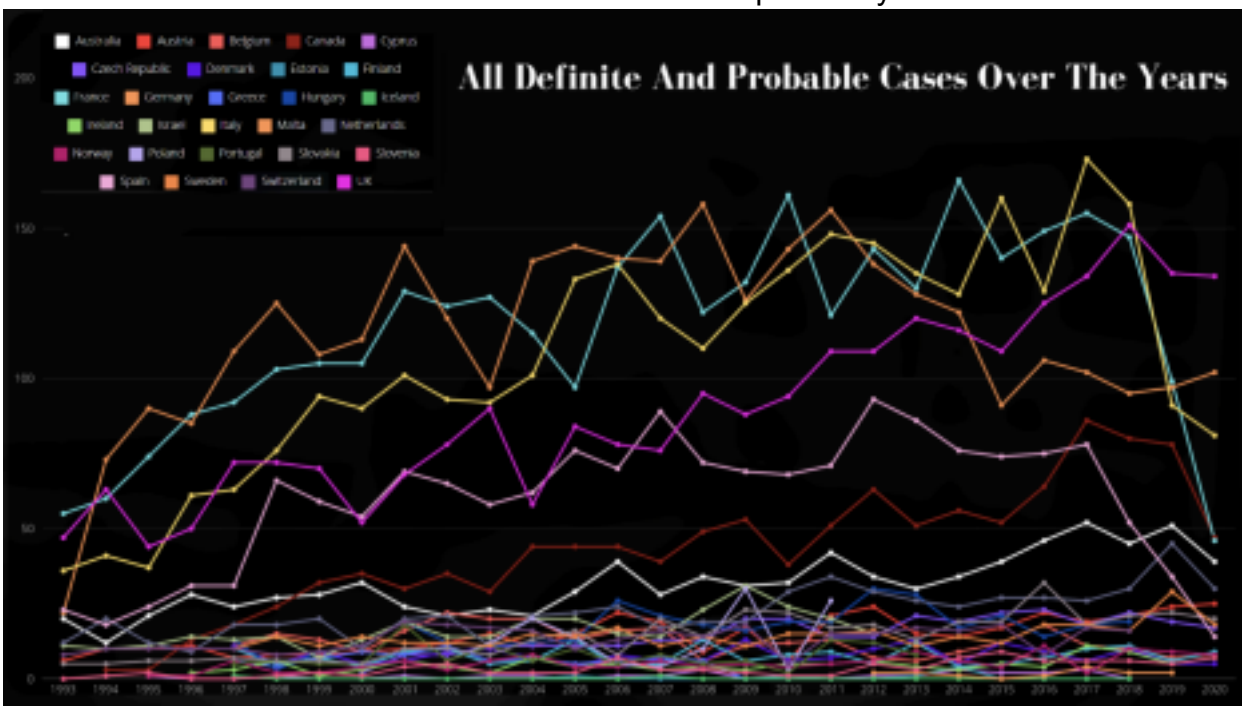
Introduction

Background & Origin

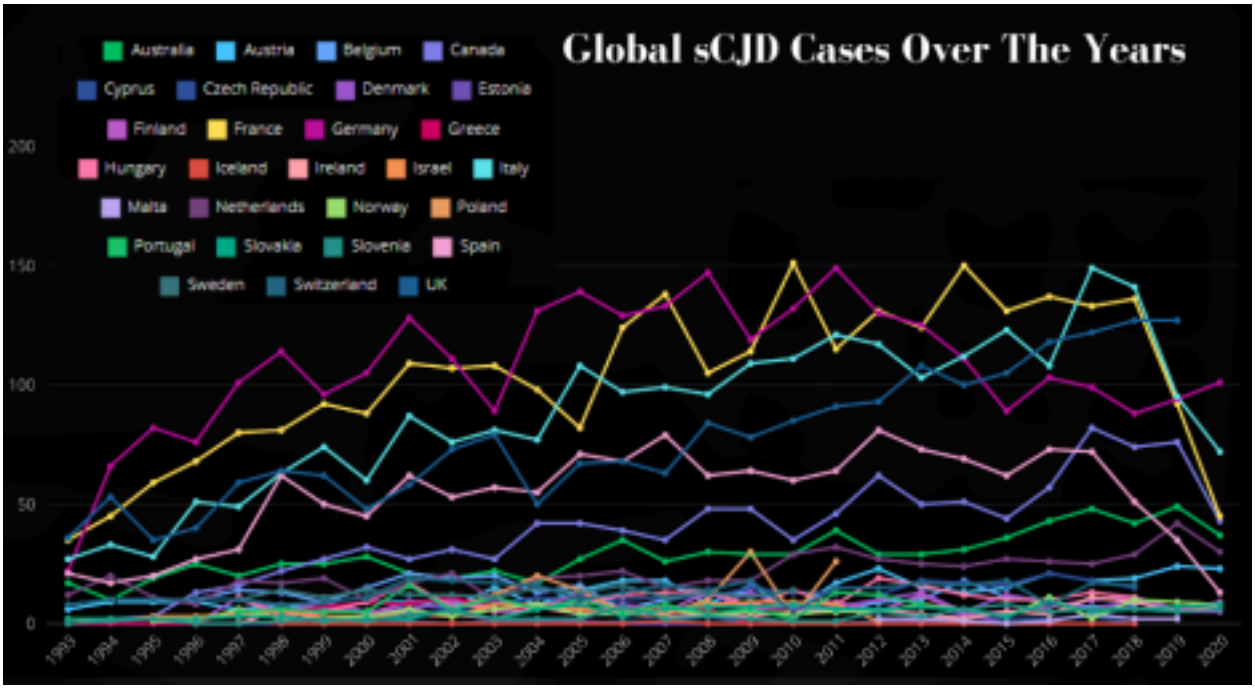
Creutzfeldt-Jakob disease (CJD) dates back to the last century. Neurologists in 1920 by the names of Hans Gerhard Creutzfeldt and Alfons Maria Jakob independently discovered the rare disorder with observations of rapid progress regarding dementia and muscle stiffness. Creutzfeldt and Jakob observed this disease by conducting clinical examinations of patients who were showing symptoms; these symptoms were uncommon to any previously identified diseases. Cognitive impairments shown in the results led both neurologists to conduct further post-mortem examinations. These examinations, familiarly called autopsies, were done on deceased patients who had symptoms of this disease during their lifetime. These neurologists further looked into changes in the brain tissue of the patients as well as vacuole formation in the brain called spongiform degeneration. The first case of this disease was not medically recorded. However, a subtype, variant CJD (vCJD) was first recognized in the United Kingdom in 1996. This variant is also known to be linked with the epidemic of bovine spongiform encephalopathy (BSE) commonly known as Mad Cow disease.

Transmission & Global Health

There are only around 1 million to 2 million reported incidents annually, with 85% of the cases being sCJD. With the UK having the first recorded vCJD case, its sizable portion of cases is understandable. However, concluding observations from the data are uncertain due to the randomness and abundance of the sCJD variant comparatively.



The causes and transmission of CJD vary significantly based on the variant. 1) The sCJD variant occurs worldwide without a known cause. There are no signs of physical transmittance, and the condition is believed to occur randomly within the brain. The research team employed CSV files to chart instances of sCJD across various countries, ultimately determining that cases are widely dispersed. Despite some trends, no significant attribution to any specific country could be concluded. Further research on brain cells, prion proteins, and the pathology of CJD could help us understand why some prion proteins spontaneously fold incorrectly, and environmental factors that could be a cause and help us take more preventable measures.

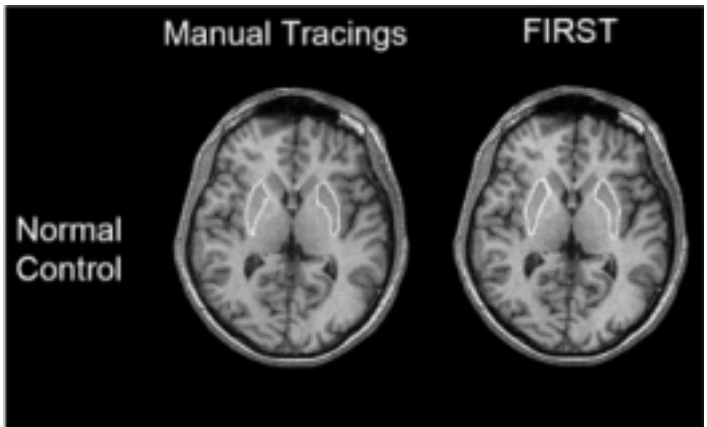


The fCJD variant is caused by genetic mutations in the prion protein gene (PRNP). These mutations are inherited in an autosomal dominant pattern, meaning they will always be inherited even by a singular copy of the gene. While a concrete connection has yet to be made, the higher prevalence among Africans may suggest genetic susceptibility. However, further research needs to be conducted to rule out the consequence of genetic diversity in the region, potentially due to increased reproductive activity.

The aCJD variant can be classified into three forms: Kuru, Iatrogenic CJD (iCJD), or Variant CJD (vCJD). Kuru, now extinct, used to be prevalent among the Fore linguistic group in Papua New Guinea. The extinction is likely from the stopped ritualistic practice of cannibalism, and possible built-up immunity. Understanding immunity could contribute to finding a vaccine or cure, and help our overall understanding of neurological diseases. iCJD can be acquired through unsanitary medical equipment, leading to contamination. vCJD is transmitted through the consumption of contaminated beef, injection of blood transfusion, or injection of plasma transfusions.

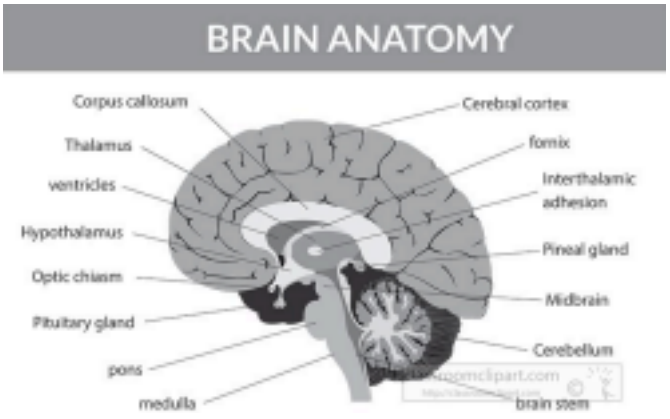
Analysis & Results

Effect on Hypothalamus & Pituitary Gland



The origin site of CJD and the misfolded proteins in the brain has yet to be confirmed, however, spongiform degeneration occurs primarily in the cerebral cortex, indicating a correlation with this region. After the production of one misfolded protein, the condition spreads among other brain cells

primarily through self-aggregation, a process in which segments of the protein typically tucked away in the protein structure are exposed, and make contact with the solvent (cerebrospinal fluid). This leads to increased adhesion which causes the prion proteins to clump up and aggravate contamination. This over-accumulation of abnormal proteins disrupts homeostasis, leading to eventual apoptosis. As the brain cells die, neurons in the cells die as well, leading to the formation of empty vacuoles and the loss of brain volume. As the condition worsens, the deterioration of the brain can spread to areas like the Hypothalamus and Pituitary gland. From the MRI scan of a control brain versus a CJD-affected brain, we can see a noticeable reduction in the central area of the brain where the pituitary gland and hypothalamus are located. These vacuoles, indicative of neuronal loss and tissue degeneration, highlight the destructive impact of CJD on these brain regions critical to the endocrine system.



Labeled Brain (Anatomy Gray and White Clipart - human-brain-anatomy-labeled-gray-color)

Hormonal Effects

The interplay of the gonadotropin-releasing hormone (GnRH), the follicle-stimulating hormone (FSH), and the luteinizing hormone (LH) orchestrated by the pituitary gland constitutes a pivotal regulatory system governing the onset and progression of puberty. In men, the following hormones cause testicles to produce testosterone while in women it causes the ovaries to produce estrogen and progesterone. By producing essential sex hormones, the hormones exert profound effects on sexual maturity, libido, and fertility.

Two of the main agents involved in stopping the pituitary gland from secreting vital sex hormones are GnRH agonists and GnRH antagonists, which can be found in commonly used drugs. GnRH agonists activate the pituitary gland to generate more FSH and luteinizing hormone. Over time, continued use of the drug can stop the creation of both hormones altogether. GnRH antagonists prevent the pituitary gland from responding to GnRH, stopping the production of luteinizing hormones and sex hormones.

Although CJD can not be entirely treated, several medications can help combat its side effects. For example, Antiepileptic drugs can be administered to the patient to manage seizures as well as violent outbursts. Two of these drugs include benzodiazepines (BZDs) and clonazepam

(CZP). They can serve as crucial agents in managing epilepsy and shock-induced seizures, serving as the prime solution to combat CJD seizures.

BZDs are first-choice medications for addressing status epilepticus and seizures stemming from post-anoxic injury. Additionally, they are commonly utilized to treat febrile seizures and acute repetitive seizures. The clinical benefits of this medication include its rapid onset of effect, high rates of efficacy, and minimal toxicity. CZPs belong to a branch of BZDs.

Although provided to have multiple benefits, healthcare professionals should consider opting for different Antiepileptic drugs such as Levetiracetam. Levetiracetam is used to

treat seizures in epilepsy by slowing the bursts of electrical activity that seizures send to the brain, temporarily affecting how it functions.

Levetiracetam essentially works by decreasing the amount of glutamate, which is an excitatory neurotransmitter, released into the synapse. Glutamate is known to play a significant role in promoting neuronal excitability. Excessive glutamate release leads to seizures. By reducing glutamate release through its effects on calcium channels and synaptic vesicle protein 2A, Levetiracetam helps stabilize neuronal activity as well as decrease the likelihood of seizures occurring.

The first way in which Levetiracetam prevents excessive glutamate release is through the inhibition of calcium channels. Levetiracetam blocks N-type calcium channels found on the presynaptic neuron. By doing so, it prevents the entry of calcium ions into the neuron. Calcium influx is crucial for the release of neurotransmitters, including glutamate, from synaptic vesicles. Thus, by inhibiting calcium channels, levetiracetam reduces and controls the amount of glutamate released into the synapse.

The second way in which the drug controls glutamate release is by modulating the Synaptic Vesicle Protein 2A (SV2A). SV2A is a protein that is involved in the process of releasing neurotransmitters from synaptic vesicles. By modulating SV2A, Levetiracetam further inhibits the release of glutamate from intracellular vesicles.

Levitaracetam also has several limitations, however. First, being a name-brand drug it is more costly than standard epilepsy-treating drugs. Levetiracetam, being a recent drug that has appeared in the medical realm, has proven to be more costly than previously existing drugs. Because it is highly novel, it is more in demand than already existing, researched drugs for epilepsy. Cost considerations could deter healthcare providers from prescribing Levetiracetam if they perceive it as less cost-effective or if patients cannot afford it.

Additionally, many don’t prescribe the drug because of its availability and alternate treatment options. Since the drug has not been thoroughly researched, it may be scarce in some areas and unsafe to prescribe just yet. Regulatory approvals for medication could also dictate their authorized indications. Healthcare professionals may hesitate to prescribe medications off-label without having adequate evidence of efficacy as well as safety. As a result, they tend to rely on and administer previously tested antiepileptic drugs such as CZPs and BZDs, especially for CJD.

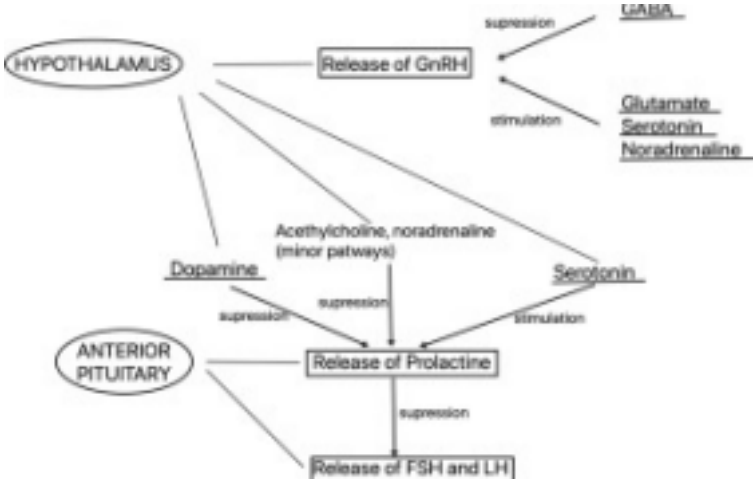
Given the limitations, patients should consider opting for Levetiracetam as a prime antiepileptic drug for CJD. It is one of the only antiepileptic drugs proven to not affect and alter hormonal secretion. In a case study to monitor the drug responses, a set of males were administered levetiracetam and the responses were recorded. Each subject went through an assessment of hormones (estradiol, testosterone, prolactin, FSH, LH) as well as sperm parameters (sperm count, morphology, and motility) and responses

were recorded before and after the mean of the 13.7-week trial of treatment with Levetiracetam. At the end of the study, the conclusion was clear: there were no significant changes in measured hormonal levels. This is in contradistinction to older AEDs (automated external defibrillators)–which are used to deliver shocks to ventricular fibrillation patients–and other antiepileptic drugs.

As a means to work towards avoiding vital hormonal secretion alteration, we can further research the administration of Levetiracetam as a prime antiepileptic drug. Steering away from first-choice antiepileptic drugs such as BZDs and CZPs can prove to be extremely crucial. Although it is more costly, health professionals should consider researching the drug further to use it as the key drug to treat CJD-induced seizures. This can not only help limit the effect on vital hormonal secretions, affecting the hypothalamus and the endocrine system as a whole but also prevent imposed risks of it such as infertility. Working towards eliminating the external factors of the body that CJD affects, apart from the brain, can put society a step further in the medical realm to eventually find a cure for CJD overall.

After testing central and peripheral BZD serums on male rats, it was proven that these prime antiepileptic drugs can intertwine with vital hormone secretion. Clonazepam was found to increase hormone levels at 0.2 mg/kg while FG 7142 (a benzodiazepine partial inverse agonist) was found to decrease growth hormone levels. The results of the study had a common theme: they affected the generation of sex hormones severely.

Administering the drugs directly correlates to the workings of the hypothalamus by altering the release of GnRH and Prolactin, whose suppression causes the excretion of FSH and Luteinizing Hormone (LH) as seen in the labeled web diagram.



Graphical Abstract- The adverse effects of psychotropic drugs as an endocrine-disrupting chemicals on the hypothalamic-pituitary regulation in male

This proves how the drugs used to combat CJD's side effects serve as GnRH agonists and antagonists. The improper production of the hormones can lead to vacillating hormonal body responses. Additionally, it can cause irregular menstrual cycles in females and spermatogenesis in males, inversely affecting fertility rates.

Effects on Metabolic Dysfunction

The hypothalamus acts as the focal point for regulating metabolism. It receives and processes signals from the body's external organs (the periphery) and the internal nervous system to regulate important functions like energy balance. The hypothalamus adjusts the metabolic balance based on signals like insulin, blood sugar, and leptin

levels. In this disease's late stage, muscle wasting and weakness can occur causing the brain to lose connection with the motor functions. This can make basic body coordination difficult, which is imperative to how a body can function. CJD is further investigated to be the disintegration of brain tissue due to the abnormal amount of prion proteins. The prion proteins are the surface of cells that are expressed in the Central Nervous System (CNS). CrJD has an everlasting impact on motor dysfunction which can lead to the body being immobile. Due to this disease being life-threatening and no current cure as of today when you are detected with CJD you will spend the remainder of your life bedridden. The accumulation of these prion proteins can further damage the normal cellular processes.

The Future/Therapeutic Interventions

The following is a simulation created by the research group that models the accumulation of the total number of CJD cases for some years after 2023. The simulation helps us understand the continuing trend as well as how potential methods, which will be discussed later in the paper, affect this trend and could potentially result in a decline in CJD cases.

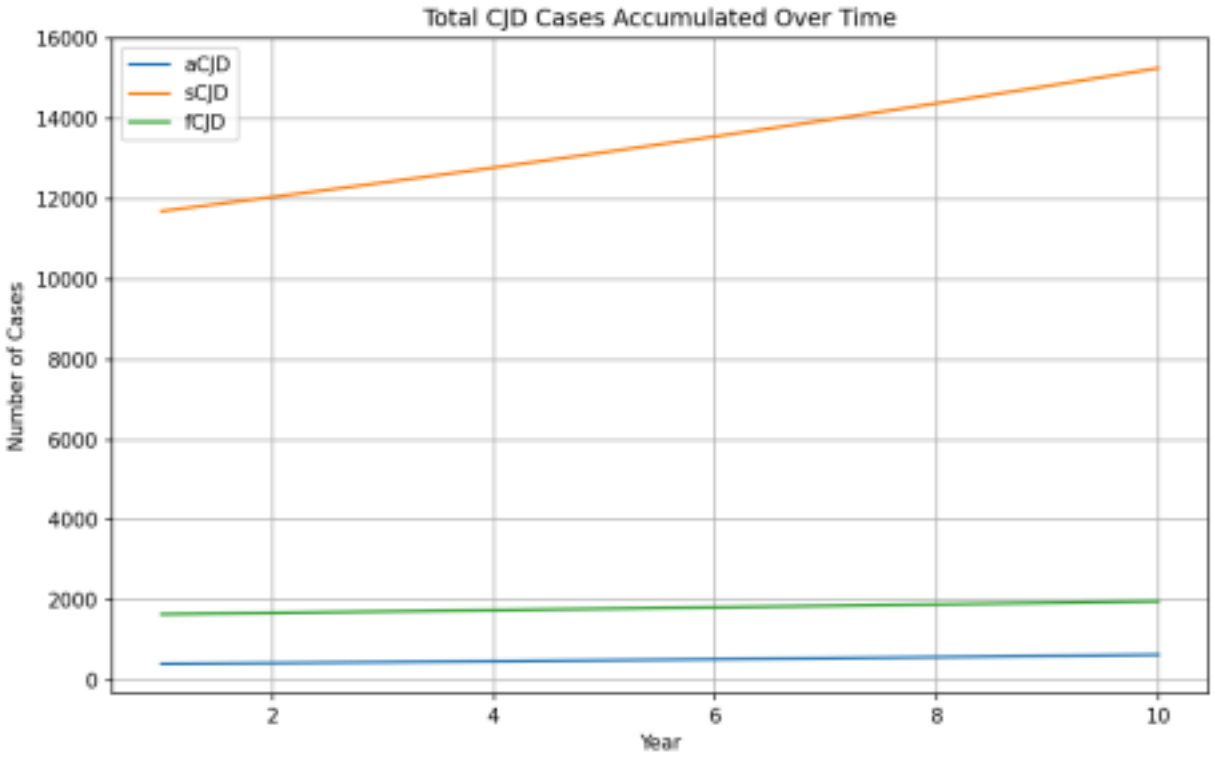
This simulation was created through Python with help from libraries such as matplotlib, pandas, and numpy which helped with the manipulation and visualization of the data. In addition, it also created a projected data sheet with values of aCJD, sCJD, and fCJD cases through a tailored algorithm embedded in the program. We used a data set from the University of Edinburgh to find out the number of cases before 2023. Data after was produced by the simulation.

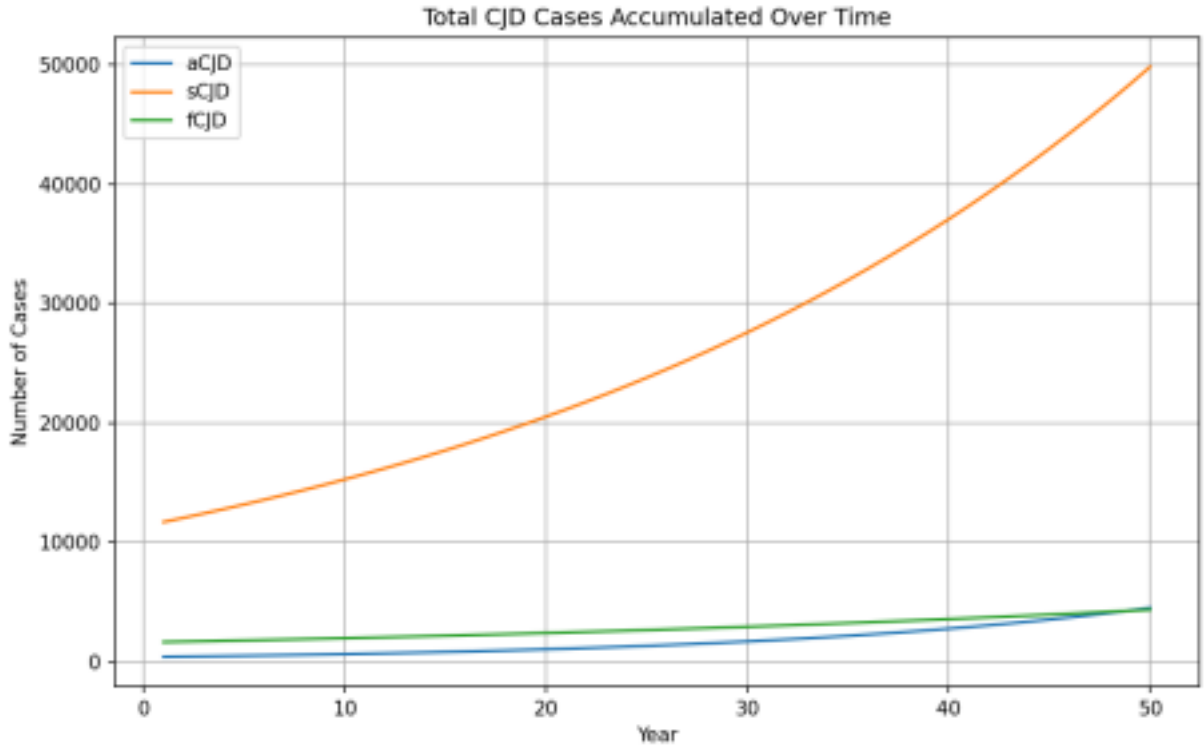
```
for year in range(1, num_years):
    aCJD_cases[year] = aCJD_cases[year - 1] * (1 + growth_rate_aCJD)
    sCJD_cases[year] = sCJD_cases[year - 1] * (1 + growth_rate_sCJD)
    fCJD_cases[year] = fCJD_cases[year - 1] * (1 + growth_rate_fCJD)

# print data values
print("Year\taCJD\t\tsCJD\t\tfCJD")
for year in range(num_years):
    print(f"{year+1}\t\t{int(aCJD_cases[year]):,}\t\t{int(sCJD_cases[year]):,}\t\t\t{int(fCJD_cases[year]):,}")

# print total death_toll
chance_of_death_within_one_year = 0.98
total_cases = int(aCJD_cases[-1] + sCJD_cases[-1] + fCJD_cases[-1])
death_toll_within_num_years = str(int(total_cases * chance_of_death_within_one_year))

print("")
#print("death_toll within one year for " + str(num_years) + " years: " + death_toll_within_num_years)
print("total death_toll: " + str(total_cases))

# graph

data = {'Year': years, 'aCJD': aCJD_cases, 'sCJD': sCJD_cases, 'fCJD': fCJD_cases}
```

```
# graph

data = {'Year': years, 'aCJD': aCJD_cases, 'sCJD': sCJD_cases, 'fCJD': fCJD_cases}
df = pd.DataFrame(data)

plt.figure(figsize=(10, 6))
#plt.style.use('dark_background')
plt.plot(df['Year'], df['aCJD'], label='aCJD')
plt.plot(df['Year'], df['sCJD'], label='sCJD')
plt.plot(df['Year'], df['fCJD'], label='fCJD')
plt.xlabel('Year')
plt.ylabel('Number of Cases')
plt.title('Total CJD Cases Accumulated Over Time')
plt.legend()
plt.grid(True)
plt.show()
```

(snippets from PyCharm IDE)

Below are predictions the simulation made for some 10 and 50 years, respectively:





Below are snippets of the chart created as well as the predicted death toll:

3	455	12,413	1,717
4	478	12,785	1,752
5	502	13,169	1,787
6	527	13,564	1,822
7	553	13,971	1,859
8	581	14,390	1,896
9	610	14,822	1,934
10	640	15,267	1,973

total death_toll: 17880

43	3,205	40,493	3,792
44	3,365	41,708	3,868
45	3,534	42,959	3,945
46	3,710	44,248	4,024
47	3,896	45,575	4,105
48	4,091	46,943	4,187
49	4,295	48,351	4,271
50	4,510	49,802	4,356

total death_toll: 58669

After the simulation, our team came up with multiple methods that might help mitigate the reflected death toll:

Method 1: As of 2024 almost all hospitals use procedures in which contamination is nonexistent. However, it's the keyword that contributes to the promotion of aCJD through medical offices. In many parts of the world, medical treatment/care is neglected, insufficiently carried out, or irrevocable without external improvement. To combat this, imperative measures must be carried out to properly clean, supply, and manufacture medical conduct in areas of the world that are lacking.

Method 2: Cases of fCJD are passed down generations through reproduction where certain DNA for misfolded proteins are inherited in the offspring. Despite being severe, a preventative measure towards discontinuing the trend of CJD through inheritance would be to restrict reproducing if one is known to have CJD. However, this method is controversial and raises ethical concerns.

Method 3: Another major part of aCJD is from consuming meat, especially through animals that have contracted the disease. Reform in the industry began in 1906 via The Federal Meat Inspection Act. More legislation has been passed both federally and through the state succeeding 1906. While continued efforts are being made to improve sanitation and overall

methods of meat packing, it's ultimately more detrimental to continue improving the meat standards than to hold off. Increasing the projected precautions in factories has the opposite effect on the number of lives one could save as it would take more time, resources, and energy to produce and manufacture meat. This would lead to a deficiency of meat in the consumer's hands as well as soar in prices. For example, if we instituted a practice of scanning each cow before butchery, it would require millions of dollars to get equipment and would cause a slower rate of production causing inefficiency.

Below are the trends and death tolls reflected after implementing our methods for 10, and 50 years respectively:

3	421	12,413	1,667
4	425	12,785	1,675
5	429	13,169	1,684
6	434	13,564	1,692
7	438	13,971	1,701
8	442	14,390	1,709
9	447	14,822	1,718
10	451	15,267	1,726

total death_toll: 17445

43	627	40,493	2,035
44	633	41,708	2,045
45	639	42,959	2,056
46	646	44,248	2,066
47	652	45,575	2,076
48	659	46,943	2,087
49	665	48,351	2,097
50	672	49,802	2,108

total death_toll: 52582

Looking at our results, we can confirm that these methods did make an impact on the number of CJD cases and deaths from the disease. However, the number remains high since most CJD cases are of the sporadic variant. In addition, it's important to consider that the number of people that have died before 2023 was added to the death toll and could not be altered.

Conclusion

In conclusion, Creutzfeldt-Jakob Disease (CJD) presents a multifaceted challenge with distinct variants and complex neurological impacts, particularly on the hypothalamus and pituitary gland. Current treatments focus on symptom management, notably using antiepileptic drugs, yet these approaches do not halt disease progression or reverse neural damage. Future research should prioritize elucidating the underlying mechanisms of prion diseases, developing targeted therapies to mitigate symptoms, and ultimately striving toward effective treatments and a cure. This research underscores the urgent need for continued investigation into CJD to improve patient outcomes and advance our understanding of neurodegenerative disorders.

Acknowledgments

Special thanks to Sahaj Satani and his team from MEDILOQUY for his invaluable assistance in editing and refining this research paper to what it looks like now.

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